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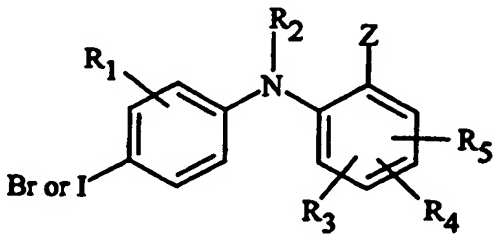
(54) Title: 2-(4-BROMO OR 4-IODO PHENYLAMINO) BENZOIC ACID DERIVATIVES AND THEIR USE AS MEK INHIBITORS

(57) Abstract

Phenylamino benzoic acid, benzamides, and benzyl alcohol derivatives of formula (I) where R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen or substituent groups such as alkyl, and where R_7 is hydrogen or an organic radical, and Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, or CH_2OR_7, are potent inhibitors of MEK and, as such, are effective in treating cancer and other proliferative diseases such as inflammation, psoriasis and restenosis, as well as stroke, heart failure, and immunodeficiency disorders.



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2-(4-BROMO OR 4-IODO PHENYLAMINO) BENZOIC ACID DERIVATIVES AND THEIR USE AS MEK INHIBITORS

FIELD OF THE INVENTION

This invention provides benzoic acid and amide derivatives of anthranilic acids which inhibit certain dual specificity kinase enzymes involved in proliferative diseases such as cancer and restenosis.

BACKGROUND OF THE INVENTION

Proliferative diseases are caused by a defect in the intracellular signaling system, or the signal transduction mechanism of certain proteins. Cancer, for example, is commonly caused by a series of defects in these signaling proteins, resulting from a change either in their intrinsic activity or in their cellular concentrations. The cell may produce a growth factor that binds to its own receptors, resulting in an autocrine loop, which continually stimulates proliferation. Mutations or overexpression of intracellular signaling proteins can lead to spurious mitogenic signals within the cell. Some of the most common mutations occur in genes encoding the protein known as Ras, which is a G-protein that is activated when bound to GTP, and inactivated when bound to GDP.

The above mentioned growth factor receptors, and many other mitogenic receptors, when activated, lead to Ras being converted from the GDP-bound state to the GTP-bound state. This signal is an absolute prerequisite for proliferation in most cell types. Defects in this signaling system, especially in the deactivation of the Ras.GTP complex, are common in cancers, and lead to the signaling cascade below Ras being chronically activated.

Activated Ras leads in turn to the activation of a cascade of serine/threonine kinases. One of the groups of kinases known to require an active Ras.GTP for its own activation is the Raf family. These in turn activate MEK, (eg, MEK_1 and MEK_2) which then activates MAP kinase. Activation of MAP kinase by mitogens appears to be essential for proliferation, and constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream

Ras signaling, for example by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants. Although Ras is not itself a protein kinase, it participates in the activation of Raf and other kinases, most likely through a phosphorylation mechanism. Once activated, Raf and other kinases phosphorylate MEK on two closely adjacent serine residues, S^{218} and S^{222} in the case of MEK-1, which are the prerequisite for activation of MEK as a kinase. MEK in turn phosphorylates MAP kinase on both a tyrosine, Y^{185}, and a threonine residue, T^{183}, separated by a single amino acid. This double phosphorylation activates MAP kinase at least 100-fold, and it can now catalyze the phosphorylation of a large number of proteins, including several transcription factors and other kinases. Many of these MAP kinase phosphorylations are mitogenically activating for the target protein, whether it be another kinase, a transcription factor, or other cellular protein. MEK is also activated by several kinases other than Raf-1, including MEKK, and itself appears to be a signal integrating kinase. As far as is currently known, MEK is highly specific for the phosphorylation of MAP kinase. In fact, no substrate for MEK other than MAP kinase has been demonstrated to date, and MEK does not phosphorylate peptides based on the MAP kinase phosphorylation sequence, or even phosphorylate denatured MAP kinase. MEK also appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Both this requirement and the unusual specificity of MEK are suggestive that it may have enough difference in its mechanism of action to other protein kinases that selective inhibitors of MEK, possibly operating through allosteric mechanisms rather than through the usual blockade of the ATP binding site, may be found.

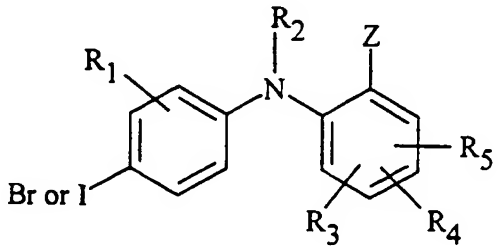
This invention provides compounds which are highly specific inhibitors of the kinase activity of MEK. Both in enzyme assays and whole cells, the compounds inhibit the phosphorylation of MAP kinase by MEK, thus preventing the activation of MAP kinase in cells in which the Ras cascade has been activated. The results of this enzyme inhibition include a reversal of transformed phenotype of some cell types, as measured both by the ability of the transformed cells to

grow in an anchorage-independent manner and by the ability of some transformed cell lines to proliferate independently of external mitogens.

The compounds provided by this invention are 2-(phenylamino) benzoic acid, tetrazole, ester, amide, and benzyl alcohol derivatives, in which the phenyl ring is substituted at the 4-position with bromo or iodo. United States Patent No. 5,155,110 discloses a wide variety of fenamic acid derivatives, including certain 2-(phenylamino) benzoic acid derivatives, as anti-inflammatory agents. The reference fails to describe the compounds of this invention or their kinase inhibitory activity.

SUMMARY OF THE INVENTION

This invention provides 4-bromo and 4-iodo phenylamino benzoic acid derivatives which are selective MEK kinase inhibitors and as such are useful for treating proliferative diseases such as cancer, psoriasis, and restenosis. The compounds are defined by Formula I



I

wherein:

R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_2 is hydrogen;

R_3, R_4, and R_5 independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or $-(O \text{ or } NH)_m-(CH_2)_n-R_9$, where R_9 is hydrogen, hydroxy, CO_2H, or $NR_{10}R_{11}$;

n is 0-4;

m is 0 or 1;

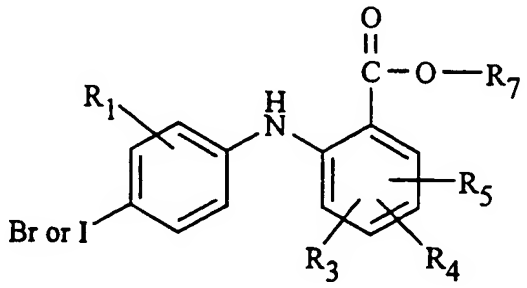
R_{10} and R_{11} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached, can complete a 3-10 member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7;

R_6 and R_7 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C-C_1-C_8 alkyl, aryl, heteroaryl, C_3-C_{10} cycloalkyl, or C_3-C_{10} (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R_6 and R_7 together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl;

and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, and the pharmaceutically acceptable salts thereof.

Preferred compounds have Formula II

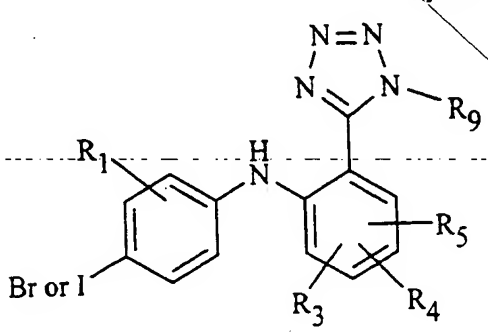


II

where R_1, R_3, R_4, R_5, R_6, and R_7 are as defined above. Especially preferred are compounds wherein R_1 is methyl or halo, and R_3, R_4, and R_5 are halo such as fluoro or bromo.

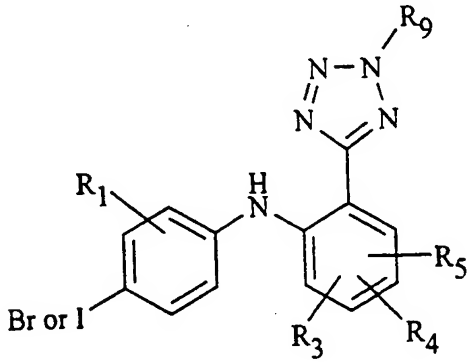
The compounds of Formula
and are esters when R7 is other than hy
to the acids in physical and biological proper
Formula IIa

when R7 is hydrogen,
which are analogous
ivatives of

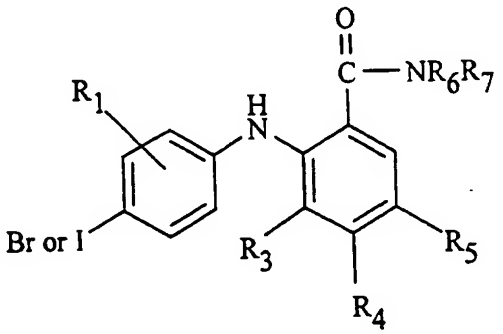


or

IIa

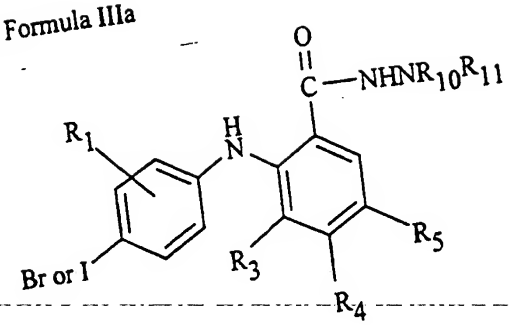


Another preferred group of compounds are amides Formula III



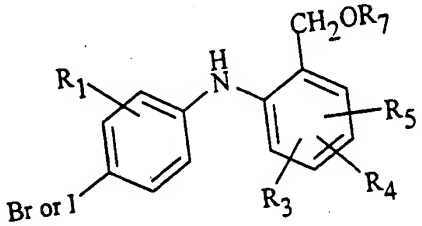
III

and hydrazides of Formula IIIa



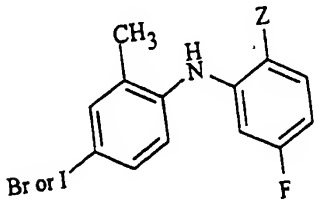
IIIa

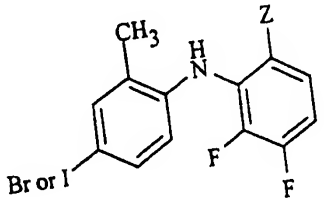
The benzyl alcohols of the invention have Formula IV

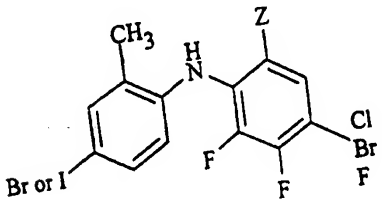


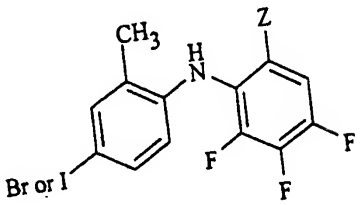
IV

The most preferred compounds are those wherein R_1 is methyl, R_3 is hydrogen or halo such as fluoro, R_4 is halo such as fluoro, and R_5 is hydrogen or halo such as fluoro, bromo, or chloro. Representative compounds have the formulas









This invention also provides pharmaceutical formulations comprising a compound of Formula I together with a pharmaceutically acceptable excipient, diluent, or carrier. Preferred formulations include any of the foregoing preferred compounds together with an excipient, diluent, or carrier.

The compounds of Formula I are potent and selective inhibitors of MEK_1 and MEK_2 kinase enzymes. They are, therefore, useful to treat subjects suffering from cancer, stroke, diabetes, Alzheimer's disease, cystic fibrosis, viral disease, heart failure, and proliferative diseases such as psoriasis, restenosis, autoimmune disease, and atherosclerosis. The compounds are especially well suited to treat cancers such as breast cancer, colon cancer, prostate cancer, skin cancer, and pancreatic cancer. They are particularly well-suited for use in conjunction with conventional radiation therapy. The compounds are also immunomodulatory agents and can be used to treat degenerative diseases where change in MEK activation leads to pathologies such as hepatomegaly and cardiomegaly. The invention provides a method of inhibiting MEK enzymes and the foregoing diseases by administering to a subject an effective amount of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "aryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from five to twelve carbon atoms. Examples of typical aryl groups include phenyl, naphthyl, and fluorenyl. The aryl may be substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Typical substituted aryl groups include 3-fluorophenyl, 3,5-dimethoxyphenyl, 4-nitronaphthyl, 2-methyl-4-chloro-7-aminofluorenyl, and the like.

The term "aryloxy" means an aryl group bonded through an oxygen atom, for example phenoxy, 3-bromophenoxy, naphthyloxy, and 4-methyl-1-fluorenyloxy.

"Heteroaryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from four to eleven carbon atoms and one, two, or three heteroatoms

selected from O, S, or N. Examples include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, xanthenyl, pyronyl, indolyl, pyrimidyl, naphthyridyl, pyridyl, benzinnidazolyl, and triazinyl. The heteroaryl groups can be unsubstituted or substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Examples of substituted heteroaryl groups include chloropyranyl, methylthienyl, fluoropyridyl, amino-1,4-benzisoxazinyl, nitroisoquinolinyl, and hydroxyindolyl.

The heteroaryl groups can be bonded through oxygen to make heteroaryloxy groups, for example thienyloxy, isothiazolyloxy, benzofuranyloxy, pyridyloxy, and 4-methylisoquinolinyloxy.

The term "C_1-C_8 alkyl" means straight and branched chain aliphatic groups having from one to eight carbon atoms, preferably one to four. Typical C_1-C_8 alkyl groups include methyl, ethyl, isopropyl, tert.-butyl, 2,3-dimethylhexyl, and 1,1-dimethylpentyl. The alkyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, as those terms are defined herein. Typical substituted alkyl groups include chloromethyl, 3-hydroxypropyl, 2-dimethylaminobutyl, and 2-(hydroxymethylamino)ethyl. Examples of aryl and aryloxy substituted alkyl groups include phenylmethyl, 2-phenylethyl, 3-chlorophenylmethyl, 1,1-dimethyl-3-(2-nitrophenoxy)butyl, and 3,4,5-trifluoronaphthylmethyl. Examples of alkyl groups substituted by a heteroaryl or heteroaryloxy group include thienylmethyl, 2-furylethyl, 6-furyloxyoctyl, 4-methylquinolyloxymethyl, and 6-isothiazolylhexyl. Cycloalkyl substituted alkyl groups include cyclopropylmethyl, 2-cyclohexyethyl, piperidyl-2-methyl, 2-(piperidin-1-yl)-ethyl, 3-(morpholin-4-yl)propyl.

"C_2-C_8 Alkenyl" means a straight or branched carbon chain having one or more double bonds. Examples include but-2-enyl, 2-methyl-prop-2-enyl, 1,1-dimethyl-hex-4-enyl, 3-ethyl-4-methyl-pent-2-enyl, and 3-isopropyl-pent-4-enyl. The alkenyl groups can be substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, aryl, aryloxy, heteroaryl, or heteroyloxy, for example

2-bromoethenyl, 3-hydroxy-2-butenyl, 1-aminoethenyl, 3-phenylprop-2-enyl, 6-thienyl-hex-2-enyl, 2-furyloxy-but-2-enyl, and 4-naphthyloxy-hex-2-enyl.

"C_2-C_8 Alkynyl" means a straight or branched carbon chain having from two to eight carbon atoms and at least one triple bond. Typical alkynyl groups include prop-2-ynyl, 2-methyl-hex-5-ynyl, 3,4-dimethyl-hex-5-ynyl, and 2-ethyl-but-3-ynyl. The alkynyl groups can be substituted as the alkyl and alkenyl groups, for example, by aryl, aryloxy, heteroaryl, or heteroaryloxy, for example 4-(2-fluorophenyl)-but-3-ynyl, 3-methyl-5-thienylpent-4-ynyl, 3-phenoxy-hex-4-ynyl, and 2-furyloxy-3-methyl-hex-4-ynyl.

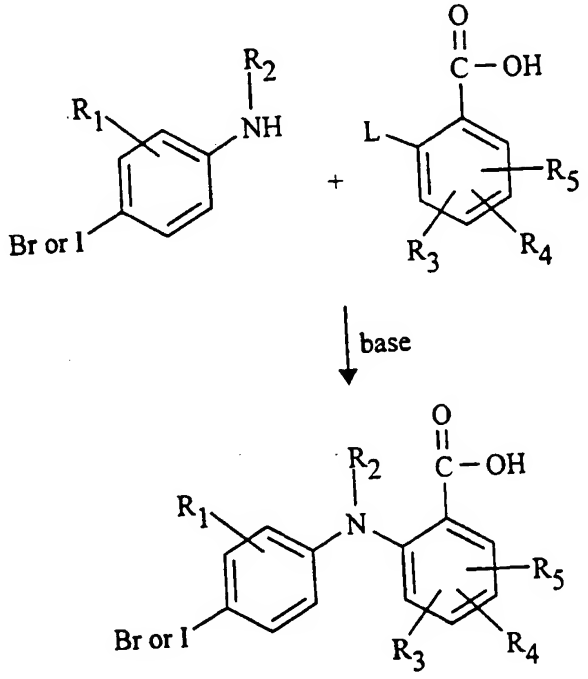
The alkenyl and alkynyl groups can have one or more double bonds or triple bonds, respectively, or a combination of double and triple bonds. For example, typical groups having both double and triple bonds include hex-2-en-4-ynyl, 3-methyl-5-phenylpent-2-en-4-ynyl, and 3-thienyloxy-hex-3-en-5-ynyl.

The term "C_3-C_{10} cycloalkyl" means a nonaromatic ring or fused rings containing from three to ten carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopenyl, cyclooctyl, bicycloheptyl, adamantyl, and cyclohexyl. The ring can optionally contain one, two, or three heteroatoms selected from O, S, or NR_9. Such groups include tetrahydrofuryl, tetrahydropyrrolyl, octahydrobenzofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, octahydroindolyl, and octahydrobenzothiofuranyl. The cycloalkyl groups can be substituted with the same substituents as an alkyl and alkenyl groups, for example, halo, hydroxy, aryl, and heteroaryloxy. Examples include 3-hydroxycyclohexyl, 2-aminocyclopropyl, 2-phenylpyrrolidinyl, and 3-thienylmorpholine-1-yl.

R_6 and R_7 can be taken together with the nitrogen to which they are attached to complete a cyclic ring having from 3 to 10 members, which may contain 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl. Examples of such cyclic rings include piperazinyl, piperidyl, pyrrolidinyl, morpholino, N-methylpiperazinyl, aziridynyl, and the like. Such rings can be substituted with halo, hydroxy, alkyl, alkoxy, amino, alkyl, and dialkylamino, aryl, aryloxy, heteroaryl, and heteroaryloxy. Typical examples include 3-hydroxy-pyrrolidinyl, 2-fluoro-piperindyl, 4-(2-hydroxyethyl)-piperidinyl, and 3-thienylmorpholino.

The 2-(4-bromo and 4-iodo phenylamino)-benzoic acid derivatives of Formula I can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a benzoic acid having a leaving group at the 2-position to give a 2-(phenylamino)-benzoic acid. This process is depicted in Scheme 1.

Scheme 1



where L is a leaving group, for example halo such as fluoro.

The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of the aniline in an unreactive organic solvent such as tetrahydrofuran or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium hydride, triethylamine, and Hunig's base. The reaction generally is carried out at a temperature of about -78°C to about 100°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the

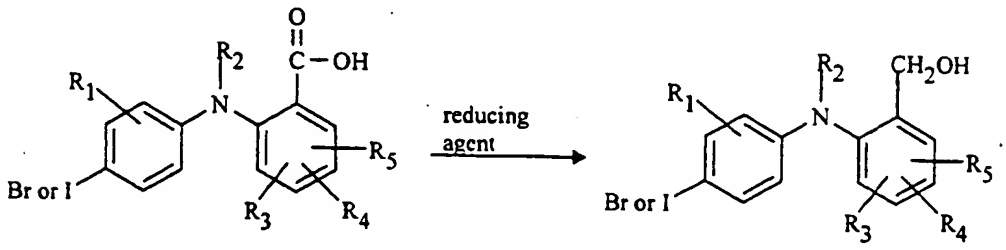
solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

The 2-(phenylamino)-benzoic acid (eg, Formula I, where R_7 is hydrogen) can be reacted with an organic or inorganic base such as pyridine, triethylamine, calcium carbonate, or sodium hydroxide to produce a pharmaceutically acceptable salt. The free acids can also be reacted with an alcohol of the formula HOR_7 (where R_7 is other than hydrogen, for example methyl) to produce the corresponding ester. Reaction of the benzoic acid with an alcohol can be carried out in the presence of a coupling agent. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBrOP), and (benzotriazolyloxy) tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and alcohol derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

The benzamides of the invention, Formula I where Z is $CONR_6R_7$, are readily prepared by reacting the foregoing benzoic acids with an amine of the formula HNR_6R_7. The reaction is carried out by reacting approximately equimolar quantities of the benzoic acid and amine in an unreactive organic solvent in the presence of a coupling reagent. Typical solvents are chloroform, dichloromethane, tetrahydrofuran, benzene, toluene, and xylene. Typical coupling reagents include DCC, EEDQ, PyBrOP, and PyBOP. The reaction is generally complete after about 10 minutes to about 2 hours when carried out at a temperature of about 0°C to about 60°C. The product amide is readily isolated by

removing the reaction solvent, for instance by evaporation, and further purification can be accomplished by normal methods such as chromatography, crystallization, or distillation. The hydrazides (z = $CONHNR_{10}R_{11}$) are similarly prepared by coupling a benzoic acid with a hydrazine of the formula $H_2HNR_{10}R_{11}$.

The benzyl alcohols of the invention, compounds of Formula I where Z is CH_2OR_6 and R_6 is hydrogen, are readily prepared by reduction of the corresponding benzoic acid according to the following scheme



Typical reducing agents commonly employed include borane in tetrahydrofuran. The reduction normally is carried out in an unreactive organic solvent such as tetrahydrofuran, and generally is complete within about 2 hours to about 24 hours when conducted at a temperature of about 0°C to about 40°C.

The following detailed examples illustrate specific compounds provided by this invention.

EXAMPLE 1

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid

To a stirring solution comprised of 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethenylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which temperature it was stirred for 2 days. The reaction mixture was concentrated.

Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and then boiled over a steambath to low volume and cooled to room temperature. The off-white fibers were collected by vacuum filtration, rinsed with hexanes, and vacuum-oven dried. (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

^1H NMR (400 MHz; DMSO): Λ 9.72 (s, 1H), 7.97 (dd, 1H, J = 7.0, 8.7 Hz), 7.70 (d, 1H, J = 1.5 Hz), 7.57 (dd, 1H, J = 8.4, 1.9 Hz), 7.17 (d, 1H, J = 8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

^{13}C NMR (100 MHz; DMSO): Λ 169.87, 167.60, 165.12, 150.17, 150.05, 139.83, 138.49, 136.07, 135.31, 135.20, 135.07, 125.60, 109.32, 105.09, 104.87, 99.72, 99.46, 89.43, 17.52;

^{19}F NMR (376 MHz; DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C = O stretch) cm^{-1};

MS (CI) M+1 = 372.

Analysis calculated for $C_{14}H_{11}FINO_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

EXAMPLES 2-30

By following the general procedure of Example 1, the following benzoic acids and salts were prepared:

Example No.	Compound	MP °C
2	3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	206-210
3	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	240.5-244.5
4	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	259.5-262
5	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	255-260
6	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	234-238

Example No.	Compound	MP °C
7	Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate	310-320 DEC
8	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	239.5-240
9	2-(2-Chloro-4-iodo-phenylamino)-5-nitro-benzoic acid	289-293
10	4-Fluoro-2-(3-fluoro-4-iodo-2-methyl-phenylamino)-benzoic acid	233-235
11	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid	264-267
12	2-(2-Fluoro-4-iodo-phenylamino)-5-nitro-benzoic acid	256-258
13	2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid	218.5-220
14	2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid	285-288 DEC
15	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid	230-234
16	3-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-221
17	3,4-Difluoro-2-(4-iodo-2-methoxy-phenylamino)-benzoic acid	230-233
18	4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	245-255 DEC
19	2-(4-Iodo-2-methyl-phenylamino)-benzoic acid	218-223
20	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	243-46
21	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	241-245
22	2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-222
23	4-Fluoro-2-(3-chloro-4-iodo-2-methyl-phenylamino)-benzoic acid	248-252.5
24	2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid	208-211
25	3-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	232-233
26	2-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	179-182
27	4-Fluoro2-(2,3-dimethyl-4-iodo-2-methyl-phenylamino)-benzoic acid	258-261
28	5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	209.5-211
29	2-Chloro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	171-175
30	2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid	251-263

EXAMPLE 31

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirring solution comprised of 0.1020 g (0.2632 mmol) of 5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid, 0.1 mL (1.7 mmol) of ethanolamine, and 0.05 mL (0.29 mmol) of diisopropylethylamine in 5 mL of a 1:1 (v/v) tetrahydrofuran-dichloromethane solution was added 0.15 g (0.29 mmol) of solid PyBOP powder directly. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The crude residue was partitioned between ether (50 mL) and 10% aqueous hydrochloric acid (50 mL). The organic phase was washed with 10% aqueous sodium hydroxide (50 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a yellow-brown oil which was crystallized from hexanes-ether to afford 0.0831 g (73%) of a green-yellow powder; mp 120-121°C;

^1H NMR (400 MHz; $CDCl_3$): δ 9.11 (s, 1H), 7.56 (d, 1H, J = 1.4 Hz), 7.46-7.41 (m, 2H), 7.20 (dd, 1H, J = 8.9, 2.4 Hz), 7.00 (t, 2H, J = 9.6 Hz), 6.55 (broad t, 1H), 3.86 (t, 2H, J = 5.0 Hz), 3.61 (dd, 2H, J = 10.1, 5.5 Hz), 2.23 (s, 3H), 1.56 (broad s, 1H);

IR (KBr) 3297 (O-H stretch), 1627 (C = O stretch) cm^{-1};

MS (CI) M+1 = 431.

Analysis calculated for $C_{16}H_{16}ClIN_2O_2$:

C, 44.62; H, 3.74; N, 6.50.

Found: C, 44.63; H, 3.67; N, 6.30.

EXAMPLES 32-48

By following the general procedure of Example 31, the following benzamides were prepared by reacting the corresponding benzoic acid with the corresponding amine.

Example No.	Compound	MP °C
32	4-Methoxy-N-(4-methoxy-phenyl)-3-nitro-benzamide	153.5-156
33	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	158
34	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide	102.5-104.5
35	N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	90-91
36	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	oil
37	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide	285-288 DEC
38	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	180-182
39	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	137-138
40	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	170-173
41	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide	69-71
42	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	132-133.4
43	N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	oil
44	4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide	122-124
45	N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	91-93
46	N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	97-99

Example No.	Compound	MP °C
47	5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	118-120
48	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	142.5-144

EXAMPLE 49

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.50 g, 1.35 mmol) was dissolved in 6 mL (6 mmol) of cold 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran solution. The reaction mixture was stirred under nitrogen atmosphere at room temperature overnight. The reaction was quenched with 80 mL of methanol. Concentration in vacuo produced a clear tan oil which was purified by MPLC. Elution with dichloromethane afforded 0.4285 g (89%) of a white solid; mp 99-100.5°C;

^{1}H NMR (400 MHz; DMSO): δ 7.57 (d, 1H, J=1.7 Hz), 7.45 (dd, 1H, J=8.4, 1.9 Hz), 7.39 (s, 1H), 7.29 (t, 1H, J=7.5 Hz), 6.89 (d, 1H, J=8.4 Hz), 6.67-6.60 (m, 1H), 5.47 (t, 1H, J=5.5 Hz), 4.49 (d, 2H, 5.1 Hz), 2.14 (s, 3H);

IR (KBr) 3372 (O-H stretch) cm^{-1};

MS (CI) M+1 = 358.

Analysis calculated for $C_{14}H_{13}FINO$:

C, 47.08; H, 3.67; N, 3.92.

Found: C, 47.17; H, 3.75; N, 3.72.

EXAMPLE 50-52

The following benzyl alcohols were prepared by the general procedure of Example 49.

Example No.	Compound	MP °C
50	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	82-85
51	[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol	126.5-128.5
52	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	60.5-63.5

Several invention compounds of Formula I were prepared utilizing combinatorial synthetic techniques. The general procedure is as follows:

To a 0.8-mL autosampler vial in a metal block was added 40 µL of a 0.5 M solution of the acid in DMF and 40 µL of the reagent amine (2M solution in Hunig's base and 1 M in amine in DMF). A 0.5M solution of PyBrop was freshly prepared and 50 µL were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm × 25 cm, 5 µM spherical silica, pore size 115 A derivatized with C-18, the sample was eluted at 4.7 mL/min with a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes). Fractions were collected by monitoring at 214 nM. The residue was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield.

EXAMPLES 53-206

The following compounds of Formula I were prepared by combinatorial methodology:

Example No.	Compound	MS M-H
53	5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	510
54	N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	462
55	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	577
56	3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	432
57	N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	444
58	3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	446
59	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	564
60	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	571
61	4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	414
62	5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	551
63	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	580
64	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	501
65	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	485

Example No.	Compound	MS M-H
66	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	493
67	N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
68	N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	460
69	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide	384
70	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	483
71	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	495
72	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	513
73	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide	480
74	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	467
75	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide	453
76	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	557
77	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	479
78	2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide	425
79	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	461
80	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	475
81	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide	445
82	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide	400

Example No.	Compound	MS M-H
83	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	437
84	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide	474
85	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide	450
86	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide	431
87	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide	444
88	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide	451
89	5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide	557*
90	5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide	541*
91	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide	487
92	5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)-benzamide	601*
93	5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	486*
94	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	497*
95	(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-	466
96	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	484*
97	5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	530*
98	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)-benzamide	518*

Example No.	Compound	MS M-H
99	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)-benzamide	562*
100	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-	499
101	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid phenethyl ester	501
102	N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide	568*
103	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-	455
104	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	460
105	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	528*
106	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	542*
107	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	468*
108	5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	472*
109	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	502*
110	5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	445*
111	5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	516*
112	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	482*
113	5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	489*
114	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	556*

Example No.	Compound	MS M-H
115	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	529*
116	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	500*
117	5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	500*
118	5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	514*
119	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	512*
120	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide	509*
121	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide	544*
122	N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	470*
123	5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	516*
124	N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	456*
125	5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429*
126	N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	484*
127	N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	511*
128	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	544*
129	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide	523*
130	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-	439

Example No.	Compound	MS M-H
131	5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	558*
132	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	484*
133	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	496*
134	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-	482
135	N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	500*
136	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	443
137	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	495*
138	N-(3-Dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	483*
139	N-(2-Diisopropylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	498*
140	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	490
141	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	506
142	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	536
143	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-thiobenzoic acid S-benzyl ester	503
144	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	476
145	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	492
146	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409

Example No.	Compound	MS M-H
147	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429
148	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	413
149	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	475
150	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	593*
151	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	567
152	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
153	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	521
154	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	440
155	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	486
156	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
157	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	459
158	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409
159	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	583
160	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	538
161	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
162	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436
163	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	469

Example No.	Compound	MS M-H
164	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	475
165	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	646
166	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	598
167	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436
168	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	565
169	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	469
170	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	473
171	N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
172	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	519
173	N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	502
174	N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	559
175	N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
176	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	581
177	2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide	500
178	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	567
179	N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	451
180	5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	467
181	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	533

Example No.	Compound	MS M-H
182	5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	511
183	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	489
184	N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	478
185	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	538
186	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	477
187	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	431
188	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	475
189	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	488
190	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	477
191	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	523
192	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
193	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	427
194	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	461
195	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	442
196	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	415
197	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
198	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411

Example No.	Compound	MS M-H
199	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	540
200	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438
201	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411
202	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	585
203	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
204	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	601
205	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	522
206	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438

* M+H

EXAMPLE 207

Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

Step a: Preparation of 5-Chloro-2-fluoro-benzaldehyde

To a solution of 1-chloro-4-fluorobenzne (13.06 g, 0.1 mol) in THF (180 mL), at -78°C, LDA (2 M solution in THF, 50 mL, 0.1 mol) was added dropwise. After stirring at -78°C for 1.5 hours, DMF (8 mL) was added to the reaction mixture and allowed to warm up to room temperature overnight. The reaction mixture was partitioned between water and Et_2O. The Et_2O layer was dried ($MgSO_4$) and the solvent removed in vacuum to give 14.95 g (94%) yield of crude aldehyde:

^1H NMR ($CDCl_3$): δ, 10.3 (s, -C(=O)H).

Step b: Preparation of 5-Chloro-2-fluoro-benzaldehyde oxime

A solution of 5-chloro-2-fluoro-benzaldehyde (10 g, 0.0631 mol), hydroxylamine hydrochloride (6.57 g, 0.0946 mol) and pyridine (8.3 mL,

0.1010 mol) in EtOH (100 mL) was heated at 75°C (oil bath temperature) for 1 hour and the solvent removed under vacuum to give an oil. The oil was partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and the solvent removed under vacuum to give crude aldoxime as a solid. The solid was purified by medium pressure liquid chromatography on silica. Elution with CH_2Cl_2 gave 4.87 g (28%) of the aldoxime as white solid: mp 95-97°C; Analysis calculated for C_7H_5NOFCl:

C, 48.44; H, 2.90; N, 8.07.

Found: C, 48.55; H, 2.69, N, 7.90.

Step c: Preparation of 5-Chloro-2-fluoro-benzonirile

A solution of the 5-chloro-2-fluoro-benzaldehyde oxime (3.15 g, 0.0182 mol) in acetic anhydride (150 mL) was refluxed for 16 hours. The reaction mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (200 mL) solution. The mixture was extracted with Et_2O. The Et_2O layer was dried (K_2CO_3) and the solvent removed to give the product as an oily solid. The product was used without further purification in the next step.

Step d: Preparation of 5-(5-Chloro-2-fluoro-phenyl)-1H-tetrazole

A mixture of 5-chloro-2-fluoro-benzonitrile (2.84 g, 0.01823 mol), butanol (15 mL), sodium azide (1.543 g, 0.0237 mol), acetic acid (1.36 mL, 0.0237 mol) was refluxed for 24 hours. The reaction mixture was cooled to room temperature, additional 1.543 g sodium azide added, and the reaction mixture refluxed for additional 24 hours. After cooling to room temperature, Et_2O (100 mL) and 10% aqueous NaOH (200 mL) were added sequentially. The mixture was vigorously stirred. The aqueous layer was separated, cooled with ice-methanol bath (-15°C) and acidified to pH 1 with conc. HCl. A gray solid precipitated. The solid was dried in vacuum at 50°C to give 1.76 g (49%) of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole: mp partial melt at 110°C, complete melting at 124°C);

^1H (400 Mz, $CDCl_3$): δ 8.19-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.61-7.52 (m, 1H);

^{13}C (100 Mz, $CDCl_3$): δ 159.00, 156.49, 140.88, 133.02, 132.93, 130.73, 129.23, 129.21, 129.08, 126.05, 118.96, 118.73, 114.50;
MS (CI) M+1 = 199 (100), M = 198 (6).

Step e: Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

To a solution of 2-methyl-4-iodoaniline (3.52 g, 0.0151 mol) in THF (25 mL) at -78°C, LDA (2 molar solution in THF, 11.33 mL, 0.02267 mol) was added dropwise. After stirring for 0.5 hours, a solution of 1-(tetrazol-5-yl)-2-fluoro-5-chlorobenzene (1.5 g, 0.00756 mol) in THF (15 mL) was added dropwise. The reaction was stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous conc. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent removed giving a crude product as an oil. The oil with CH_2Cl_2->CH_2Cl_2:MeOH (9.7:0.3) gave 1.5 g (48%) of the desired product:
mp 205-208;
^1H (400 Mz, DMSO): δ 9.13 (s, 1H), 8.00-7.99 (s, 1H), 7.69 (s, 1H), 7.55-7.52 (m, 1H), 7.43-7.40 (m, 1H), 7.12-7.05 (m, 1H), 2.24 (s, 3H);
^{13}C (100 Mz, $CDCl_3$): δ 141.87, 139.28, 138.88, 135.47, 133.71, 131.65, 128.15, 123.69, 121.94, 116.68, 87.79, 17.22;
MS (CI) M+2 = 413 (44), M+1 = 412 (85), M = 411 (100).
Analysis calculated for $C_{14}H_{11}N_5ClI \cdot 0.5H_2O$:
C, 39.97; H, 2.87; N, 16.65.
Found: C, 38.87, H, 2.77; N, 16.47.

The following tetrazole substituted phenylamines were prepared by following the general procedure of Example 207.

EXAMPLE 208

(4-Iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine, mp 231°C (dec)

EXAMPLE 209

[4-Nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine, mp 205-208°C.

The invention compounds are useful in treating cancer and other proliferative diseases by virtue of their selective inhibition of the dual specificity protein kinases MEK_1 and MEK_2. The invention compound has been evaluated in a number of biological assays which are normally utilized to establish inhibition of proteins and kinases, and to measure mitogenic and metabolic responses to such inhibition.

EXAMPLES 210-224

Additional invention compounds which were prepared by the general methods described above are:

Example No.	Compound	MP °C
210	2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-4-(2-morpholin-4-yl-ethylamino)-5-nitro-benzoic acid	239-241 DEC
211	4-Amino-2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid	>270
212	2,4-Bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid	>265 DEC
213	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzoic acid	218-225 DEC
214	2-(2,6-Difluoro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid	247-249
215	2-(2-Chloro-4-iodo-phenylamino)-4-nitro-benzoic acid	267-269
216	2-(2,4-Diiodo-phenylamino)-4-fluoro-benzoic acid	260-261
217	2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-benzoic acid	259-262
218	4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid	215-217

Example No.	Compound	MP °C
219	2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-benzoic acid	242-247
220	5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid	312.5-318
221	2,3,5-Trifluoro-6-(4-iodo-2-methyl-phenylamino)-4-(4-methyl-piperazin-1-yl)-benzoic acid methyl ester dihydrofluoride salt	118-121
222	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-methyl-piperazin-1-yl)-benazmide	214-217 DEC
223	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid N',N'-dimethyl-hydrazide	154-175 DEC
224	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide	153.5-156

Enzyme Assays

Cascade assay for inhibitors of the MAP kinase pathway

Incorporation of ^{32}P into myelin basic protein (MBP) was assayed in the presence of a glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) and a glutathione S-transferase fusion protein containing p45MEK (GST-MEK). The assay solution contained 20 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 1 mM $MnCl_2$, 1 mM EGTA, 50 µM [γ-^{32}P]ATP, 10 µg GST-MEK, 0.5 µg GST-MAPK and 40 µg MBP in a final volume of 100 µL. Reactions were stopped after 20 minutes by addition of trichloroacetic acid and filtered through a GF/C filter mat. ^{32}P retained on the filter mat was determined using a 1205 Betaplate. Compounds were assessed at 10 µM for ability to inhibit incorporation of ^{32}P.

To ascertain whether compounds were inhibiting GST-MEK or GST MAPK, two additional protocols were employed. In the first protocol, compounds

were added to tubes containing GST-MEK, followed by addition of GST-MAPK, MBP and [γ-^{32}P]ATP. In the second protocol, compounds were added to tubes containing both GST-MEK and GST-MAPK, followed by MBP and [γ-^{32}P]ATP. Compounds that showed activity in both protocols were scored as MAPK inhibitors, while compounds showing activity in only the first protocol were scored as MEK inhibitors.

In vitro MAP kinase assay

Inhibitory activity was also confirmed in direct assays. For MAP kinase, 1 µg GST-MAPK was incubated with 40 µg MBP for 15 minutes at 30°C in a final volume of 50 µL containing 50 mM Tris (pH 7.5), 10 µM $MgCl_2$, 2 µM EGTA, and 10 µM [γ-^{32}P]ATP. The reaction was stopped by addition of Laemmli SDS sample buffer and phosphorylated MBP resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into MBP was determined by autoradiography, and subsequently by excision of the bands followed by scintillation counting.

In vitro MEK assay

For evaluation of direct MEK activity, 10 µg GST-MEK_1 was incubated with 5 µg of a glutathione S-transferase fusion protein containing p44MAP kinase with a lysine to alanine mutation at position 71 (GST-MAPK-KA). This mutation eliminates kinase activity of MAPK, so only kinase activity attributed to the added MEK remains. Incubations were 15 minutes at 30°C in a final volume of 50 µL containing 50 mM Tris (pH 7.5), 10 µM $MgCl_2$, 2 µM EGTA, and 10 µM [γ-^{32}P]ATP. The reaction was stopped by addition of Laemmli SDS sample buffer and phosphorylated GST-MAPK-KA was resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into GST-MAPK-KA was determined by autoradiography, and subsequently by excision of the bands followed by scintillation counting. Additionally, an artificially activated MEK was utilized that contained serine to glutamate mutations at positions 218 and 222 (GST-MEK-2E). When these sites are phosphorylated, MEK activity is

increased. Phosphorylation of these sites can be mimicked by mutation of the serine residues to glutamate. For this assay, 5 μg GST-MEK-2E was incubated with 5 μg GST-MAPK-KA for 15 minutes at 30°C in the same reaction buffer as described above. Reactions were terminated and analyzed as above.

Whole cell MAP kinase assay

To determine if compounds were able to block activation of MAP kinase in whole cells, the following protocol was used: Cells were plated in multi-well plates and grown to confluence. Cells were then serum-deprived overnight. Cells were exposed to the desired concentrations of compound or vehicle (DMSO) for 30 minutes, followed by addition of a growth factor, for example, PDGF (100 ng/mL). After a 5-minute treatment with the growth factor, cells were washed with PBS, then lysed in a buffer consisting of 70 mM NaCl, 10 mM HEPES (pH 7.4), 50 mM glycerol phosphate, and 1% Triton X-100. Lysates were clarified by centrifugation at 13,000 × g for 10 minutes. Five micrograms of the resulting supernatants were incubated with 10 μg microtubule associated protein-2 (Map2) for 15 minutes at 30°C in a final volume of 25 μL containing 50 mM Tris (pH 7.4), 10 mM $MgCl_2$, 2 mM EGTA and 30 μM [γ-^{32}P]ATP. Reactions were terminated by addition of Laemmli sample buffer. Phosphorylated Map2 was resolved on 7.5% acrylamide gels and incorporated radioactivity determined by autoradiography and subsequent excision of the bands followed by scintillation counting.

Immunoprecipitation and antiphosphotyrosine immunoblots

To determine the state of tyrosine phosphorylation of cellular MAP kinase, cells were lysed, endogenous MAP kinase was immunoprecipitated with a specific antibody, and the resulting immunoprecipitate analyzed for the presence of phosphotyrosine as follows: confluent cells were serum-deprived overnight and treated with compounds and growth factors as described above. Cells were then scraped and pelleted at 13,000 × g for 2 minutes. The resulting cell pellet was resuspended and dissolved in 100 μL of 1% SDS containing 1 mM $NaVO_4$. Following alternate boiling and vortexing to denature cellular protein, 900 μL

RIPA buffer (50 mM Tris (pH 7.4), 150 mM NaCl, 1% Triton X-100, 0.1% deoxycholate, and 10 mM EDTA) was added. To this mixture was added 60 µL agarose beads coupled with rabbit immunoglobulin G and 60 µL Pansorbin cells in order to clear the lysate of nonspecific binding proteins. This mixture was incubated at 4°C for 15 minutes then centrifuged at 13,000 × g for 10 minutes. The resulting supernatant was transferred to fresh tubes and incubated with 10 µL of a polyclonal antisera raised against a fragment of MAP kinase for a minimum of 1 hour at 4°C. Seventy microliters of a slurry of agarose beads coupled with protein G and protein A was added and the incubation continued for an additional 30 minutes at 4°C. The beads were pelleted by centrifugation at 13,000 × g for 5 minutes and washed three times with 1 mL RIPA buffer. Laemmli sample buffer was added to the final bead pellet. This mixture was boiled for 5 minutes then resolved on a 10% acrylamide gel. Proteins on the gel were transferred to a nitrocellulose membrane and nonspecific binding sites on the membrane blocked by incubation with 1% ovalbumin and 1% bovine serum albumin in TBST (150 mM NaCl, 10 mM Tris (pH 7.4), and 0.05% Tween 20). The membrane was then incubated with a commercially available antibody directed against phosphotyrosine. Antibody bound on the membrane was detected by incubation with ^{125}I-protein A, followed by autoradiography.

Cell Growth Assays

^{3}H-Thymidine incorporation

Cells were plated in multi-well plates and grown to near confluence. The media was then removed and replaced with growth media containing 1% bovine serum albumin. After 24-hour serum starvation, compounds and specific growth factors were added and incubations continued for an additional 24 hours. During the final 2 hours, ^{3}H-thymidine was added to the medium. To terminate the incubations, the medium was removed and cell layers washed twice with ice-cold phosphate-buffered saline. After the final wash, ice-cold 5% trichloroacetic acid was added and the cells incubated for 15 minutes at room temperature. The trichloroacetic acid solution was then removed and the cell layer washed three

times with distilled water. After the final wash, the cell layer was solubilized by addition of 2% sodium dodecylsulfate. Radioactivity in this solution was determined by scintillation counting.

In 3T3-L1 adipocyte cells, in which the inhibition blocks MAPK activation by insulin with an IC_{50} of 3 μM, the compound had no effect on the insulin stimulated uptake of radiolabeled 2-deoxyglucose, or on the insulin-stimulated synthesis of either lipid or glycogen at 10 μM concentration. This demonstrates that the inhibitor shows selectivity between the mitogenic and metabolic effects of insulin, and demonstrates that the inhibitor will show less toxicity than an inhibitor which does not show this surprising selectivity.

Monolayer growth

Cells were plated into multi-well plates at 10 to 20,000 cells/mL. Forty-eight hours after seeding, compounds were added to the cell growth medium and incubation was continued for 2 additional days. Cells were then removed from the wells by incubation with trypsin and enumerated with a Coulter counter.

Growth in soft-agar

Cells were seeded into 35-mm dishes at 5 to 10,000 cells/dish using growth medium containing 0.3% agar. After chilling to solidify the agar, cells were transferred to a 37°C incubator. After 7 to 10 days growth, visible colonies were manually enumerated with the aid of a dissecting microscope.
Order of addition experiments established that the invention compounds are inhibiting MEK and not MAP kinase. Experiments looking at the phosphorylation of a kinase defective mutant of MAP kinase as substrate (so that there can be no autophosphorylation of the MAP kinase to complicate interpretation) confirms that the inhibitor inhibits MEK with an IC_{50} essentially identical to that produced in the cascade assay.

Kinetic analysis demonstrates that the invention compounds are not competitive with ATP. Thus, they do not bind at the ATP binding site of the enzyme, which is probably the explanation as to why these compounds do not

show the nonspecific kinase inhibitory activity typical of most kinase inhibitors, which do bind at the ATP binding site and which are ATP competitive.

The in vitro and in vivo biological activity of several representative compounds of Formula I in the foregoing assays is presented in Table 1.

Table 1

Compound of	In Vitro		In Vivo (Cell Culture)	
Example No.	% Inhibition	IC_{50} μM	% Inhibition	IC_{50} μM
1		0.019		
2		0.014		3
3		0.0111		10
4		0.005		1
5		0.066		
6		0.071		
7		0.072		
8		0.086		
9		0.097		
10		0.101		
11		0.128		
12		0.135		
13		0.178		
14		0.179		
15		0.194		
16		0.323		
17		0.434		
18		0.446		
19		0.524	50% at 30 μM	
20		0.557		
21		0.569		
22		1.581	30% at 30 μM	
23		1.588		
24		1.944		
25		2.363		
26		2.609	50% at 30 μM	

Table 1

Compound of	In Vitro		In Vivo (Cell Culture)	
Example No.	% Inhibition	IC_{50} μM	% Inhibition	IC_{50} μM
27		2.269		
28		3.670		
29		5.331		
30	105			10
31		0.226		
32		0.028		
33		0.052		
34		0.098		
35		0.121		
36		0.129		
37		0.237		
38		0.412		
39		0.497		
40		0.651	30% at 30 μM	
41		0.872		
42		0.920		
43		>1.000		
44		1.481		
45		1.755		
46		1.814		
47		1.911		
48		1.945		
49		0.418		3
50		0.179		
51		0.887		
52		2.346		
53		0.047		0.54
54		0.158		
55		0.114		
57		0.399		
89		0.186		
89		0.614		

Table 1

Compound of	In Vitro		In Vivo (Cell Culture)	
Example No.	% Inhibition	IC_{50} μM	% Inhibition	IC_{50} μM
90		0.604		
91		2.071		
92		0.253		
93		0.521		
95		1.001		
96		0.374		
100		1.994		
184		0.278		
186		0.555		
187		0.561		
188		0.771		
189		0.859		
190		0.921		
191		1.355		
192		1.797		
193		2.902		
194		4.952		
195		12.831		
208		1.215		
209		1.372		
211		>0.1		
212		0.034		
213		0.062		
214		0.303		
215		0.031		
216		1.000		
217		>1.00		
218		0.051		
219		0.108		
220		0.029		
221		0.002		

Table 1

Compound of	In Vitro		In Vivo (Cell Culture)	
Example No.	% Inhibition	IC_{50} μM	% Inhibition	IC_{50} μM
222		0.085		
223		0.043		
224		0.028		

The invention compounds will be utilized to treat subjects suffering from cancer and other proliferative diseases, immunodeficiency, and certain degenerative diseases, and in need of treatment. The compounds are ideally suited to treating psoriasis, restenosis, autoimmune disease, and atherosclerosis. The compounds will generally be utilized as a pharmaceutical formulation, in which the compound of Formula I is present in a concentration of about 5% to about 95% by weight. The compounds can be formulated for convenient oral, parenteral, topical, rectal, or like routes of administration. The compound will be formulated with common diluents, excipients, and carriers routinely utilized in medicine, for instance, with polyols such as glycerin, ethylene glycol, sorbitol 70; mono- and difatty acid esters of ethylene glycol. Starches and sugars such as corn starch, sucrose, lactose, and the like, can be utilized for solid preparations. Such solid formulations can be in the form of tablets, troches, pills, capsules, and the like. Flavoring agents such as peppermint, oil of wintergreen, and the like can be incorporated.

Typical doses of active compound are those that are effective to treat the cancer or other proliferative disorder afflicting the mammal. Doses will generally be from about 0.1 mg per kilogram body weight to about 500 mg per kilogram body weight. Such doses will be administered from one to about four times a day, or as needed to effectively treat the cancer, psoriasis, restenosis, or other proliferative disorder.

A preferred method for delivering the invention compound is orally via a tablet, capsule, solution, or syrup. Another method is parenterally, especially via intravenous infusion of a solution of the benzopyran in isotonic saline or 5% aqueous glucose.

Following are typical formulations provided by the invention.

EXAMPLE 225

Preparation of 50-mg Tablets

Per Tablet		Per 10,000 Tablets
0.050 g	4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	500 g
0.080 g	lactose	800 g
0.010 g	corn starch (for mix)	100 g
0.008 g	corn starch (for paste)	80 g
0.002 g	magnesium stearate (1%)	20 g
0.150 g		1500 g

The benzoic acid, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 600 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The granules are passed through a #8 screen and dried at 120°F. The dry granules are passed through a #16 screen. The mixture is lubricated with 1% magnesium stearate and compressed into tablets. The tablets are administered to a mammal for inhibiting MEK enzymes and treating restenosis, atherosclerosis, and psoriasis.

EXAMPLE 226

Preparation of Oral Suspension

Ingredient	Amount
5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(methyl)-benzamide	500 mg
Sorbitol solution (70% NF)	40 mL
Sodium benzoate	150 mg
Saccharin	10 mg
Red dye	10 mg
Cherry flavor	50 mg
Distilled water qs ad	100 mL

The sorbitol solution is added to 40 mL of distilled water and the benzamide derivative is suspended therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 5 mg of the invention compound. The syrup is administered to a mammal for treating proliferative disease, especially breast cancer and skin cancer.

EXAMPLE 227

Preparation of Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 20.0 g of 4-fluoro-2-(4-bromo-2-methyl-phenylamino)-benzyl alcohol. The volume of the solution is adjusted to 1000 mL by addition of water for injection. The formulation is heat sterilized, filled into 50-mL ampoules each containing 2.0 mL (40 mg of 4-fluoro-2-(4-bromo-2-methyl-phenylamino)-benzyl), and sealed under nitrogen.

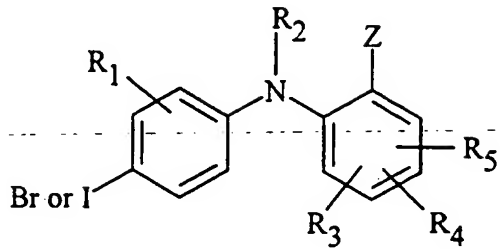
The invention compound thus formulated will be administered to a mammal in need of treatment for a proliferative disorder such as cancer, psoriasis, restenosis, atherosclerosis, autoimmune disease, and other immunodeficient diseases and degenerative disorders, at a rate and dose effective to treat the condition. An "antiproliferative amount" of an invention compound is that

quantity of compound that inhibits or reduces the rate of proliferation of target cells. Typical cancers to be treated according to this invention include breast cancer, colon cancer, prostate cancer, skin cancer, and the like. The invention compound is especially well-suited for use in combination with radiation for treating cancer. The compound is well-suited to the treatment of psoriasis, restenosis, and atherosclerosis, and to inhibiting the activity of MEK enzymes, especially MEK_1 and MEK_2. All that is required to inhibit these enzymes is to administer to a mammal an MEK inhibiting amount of a compound of the invention. An "MEK inhibiting amount" of an invention compound is an amount that when administered to a mammal causes a measurable inhibition of the MEK enzyme. Typical MEK inhibiting amounts will be from about 0.1 μg to about 500 mg of active compound per kilogram body weight. For treating the proliferative diseases mentioned above, typical doses will be from about 0.1 to about 50 mg/kg, normally given from one to about four times per day.

CLAIMS

We claim:

1. The compounds of Formula I



I

wherein:

R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_2 is hydrogen;

R_3, R_4, and R_5 independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or -(O or NH)$_m$ -$(CH_2)_n$-R_9, where R_9 is hydrogen, hydroxy, COOH, or $NR_{10}R_{11}$;

n is 0-4;

m is 0 or 1;

R_{10} and R_{11} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7;

R_6 and R_7 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $\overset{O}{\overset{\|}{C}}$-$C_1$-$C_8$ alkyl, aryl, heteroaryl, C_3-C_{10} cycloalkyl, or C_3-C_{10} (cycloalkyl optionally containing

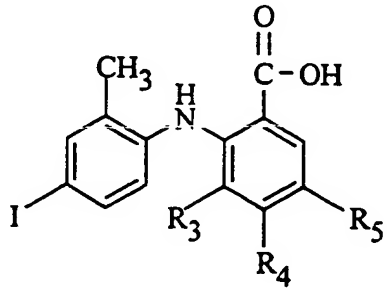
one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R_6 and R_7 together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl; and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, and the pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 wherein R_1 is CH_3 or halo.

3. A compound according to Claim 2 wherein Z is $COOR_7$, tetrazolyl, or a salt thereof.

4. A compound according to Claim 3 which is [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine; (4-Iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine; and [4-Nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine.

5. A compound according to Claim 3 having the formula



6. A compound of Claim 5 wherein R_3 is hydrogen, fluoro, or chloro; R_4 is hydrogen, fluoro, chloro, or nitro; and R_5 is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.

7. A compound of Claim 6 which is

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;

4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;

5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;

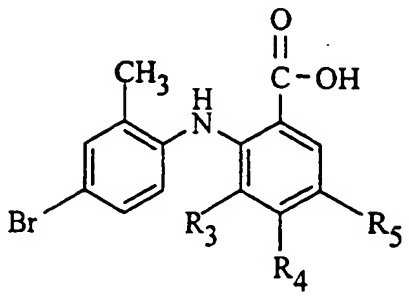
2,3,5-Trifluoro-6-(4-iodo-2-methyl-phenylamino)-4-(4-methyl-piperazin-1-yl)-benzoic acid methyl ester dihydrofluoride salt;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-methyl-piperazin-1-yl)-benazmide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid N`,N`-dimethyl-hydrazide; and

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid hydrazide.

8. A compound of Claim 3 having the formula

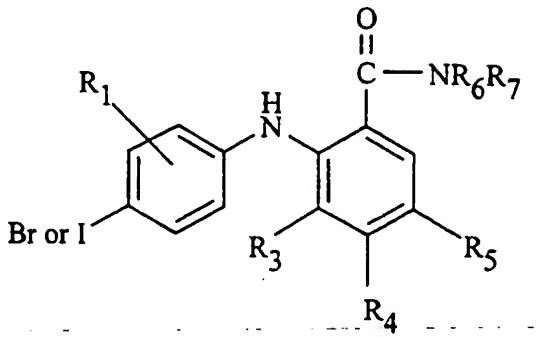


9. A compound of Claim 8 wherein R_3 is hydrogen, chloro, or fluoro; R_4 is hydrogen, chloro, fluoro, or nitro; R_5 is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.

10. A compound of Claim 1 which is
2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;
2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;
2-(2-Chloro-4-iodo-phenylamino)-3-fluoro-4-(2-morpholin-4-yl-ethylamino)-5-nitro-benzoic acid;
4-Amino-2-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid;
2,4-Bis-(2-chloro-4-iodo-phenylamino)-3-fluoro-5-nitro-benzoic acid;
2-(2-Chloro-4-iodo-phenylamino)-4-nitro-benzoic acid;
2-(2,4-Diiodo-phenylamino)-4-fluoro-benzoic acid;
2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-benzoic acid;
4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzoic acid;
2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-benzoic acid; and
5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-benzoic acid.

11. A compound of Claim 2 wherein Z is $CONR_6R_7$.

12. A compound of Claim 11 having the formula



13. A compound of Claim 12 wherein R_3 is hydrogen, chloro, or fluoro; R_4 is hydrogen, chloro, fluoro, or nitro; and R_5 is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.

14. A compound of Claim 13 which is

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide;

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide;

5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl];

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;

N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-;

5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-;

N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide; 2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

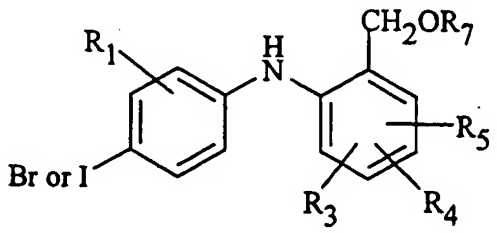
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide; and

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

15. A compound of Claim 2 wherein Z is CH_2OR_7.

16. A compound of Claim 15 having the formula



17. A compound of Claim 16 wherein: R_3 is hydrogen, chloro, or fluoro; R_4 is hydrogen, chloro, fluoro, or nitro; and R_5 is hydrogen, chloro, fluoro, bromo, nitro, or methoxy.

18. A compound of Claim 17 which is
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;
[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol; and
[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol.

19. A pharmaceutical formulation comprising a compound of Claim 1 together with a pharmaceutically acceptable excipient, diluent, or carrier.

20. A formulation of Claim 19 comprising a compound wherein Z is COOH or a salt thereof.

21. A formulation of Claim 19 comprising a compound wherein Z is $CONR_6R_7$.

22. A formulation of Claim 19 comprising a compound wherein Z is CH_2OR_7.

23. A method for inhibiting MEK enzymes in a mammal comprising administering an MEK inhibiting amount of a compound in Claim 1.

24. A method of treating a mammal suffering from a proliferative disease and in need of treatment comprising administering an antiproliferative amount of a compound of Claim 1.

25. A method according to Claim 21 wherein the proliferative disease is psoriasis, restenosis, autoimmune disease, or atherosclerosis.

26. A method according to Claim 21 wherein the proliferative disease is cancer.

27. A method for treating a mammal suffering from stroke and in need of treatment comprising administering an effective amount of a compound of Claim 1.

28. A method for treating a mammal suffering from heart failure and in need of treatment comprising administering an effective amount of a compound of Claim 1.

29. A method for treating a mammal suffering from hepatomegaly and in need of treatment comprising administering an effective amount of a compound of Claim 1.

30. A method for treating a mammal suffering from cardiomegaly and in need of treatment comprising administering an effective amount of a compound of Claim 1.

31. A method for treating a mammal suffering from diabetes and in need of treatment comprising administering an effective amount of a compound of Claim 1.

32. A method for treating a mammal suffering from Alzheimer's disease and in need of treatment comprising administering an effective amount of a compound of Claim 1.

33. A method for treating a mammal suffering from cancer and in need of treatment comprising administering an effective amount of a compound of Claim 1 in combination with conventional radiation therapy.

34. A method for treating a mammal suffering from cystic fibrosis and in need of treatment comprising administering an effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/58 C07C237/30 C07C215/68 C07C243/38 C07D257/04
C07D295/12 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 37881 A (WARNER LAMBERT) 3 September 1998 see page 3, line 16 - page 14, line 31 see page 23, line 25 - page 53, line 4 see page 72, line 1 - page 79, line 30; claims 6,7 ---	1-34
X	BEKEMEIER H ET AL: "STRUCTURE-ACTIVITY RELATIONSHIP IN NONSTEROIDAL ANTIINFLAMMATORY AGENTS, INCLUDING OSAR IN FENAMATE DERIVATIVES" AGENTS AND ACTIONS SUPPLEMENTS, 1 July 1982, pages 17-34, XP002063635 see page 25, table I, compound 15; page 24, lines 16 to 28 --- -/--	1,19,20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 1998	02/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERNER N H ET AL: "SUBSTITUTED N-PHENYLANTHRANILIC ACID HYDRAZIDES AS POTENTIAL ANTIMALARIAL AND ANTIMICROBIAL AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 13, no. 3, 1970, pages 552-554, XP002063637 see page 553, table I, compound 5; page 553, column 2 - 254, column 1 ---	1,19,20
X	R. M. ACHESON ET AL.: "The Condensation of Acridone with Tertiary Aromatic Amines and the Ultraviolet Absorption Spectra of the Products" JOURNAL OF THE CHEMICAL SOCIETY.,1956, pages 484-489, XP002081068 LETCHWORTH GB see page 488, last two lines - page 489, middle ---	1,2
X	RAMANUJAM P ET AL: "ANTIFUNGAL ACTIVITY OF SOME N-SUBSTITUTED ANTHRANILIC ACID DERIVATIVES" PLANTA MEDICA, vol. 25, no. 1, 1974, pages 43-46, XP002063636 see page 44, table I, compound 6 ---	1
X	US 2 077 249 A (FRITZ MIETZSCH ET AL.) 13 April 1937 see page 2, column 2, line 21 - line 26 ---	1
X	CHEMICAL ABSTRACTS, vol. 99, no. 19, 7 November 1983 Columbus, Ohio, US; abstract no. 158369f, M. KHALIFA ET AL.: "Synthesis and Biological Activity of Certain Derivatives of 2,4-Dioxo-1,2,3,4-tetrahydroquinazoline" page 613; column 2; XP002081073 see abstract & EGYPT. J. CHEM., vol. 25, no. 3, 1983, pages 285-291, --- -/--	1,2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropnate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 77, no. 19, 6 November 1972 Columbus, Ohio, US; abstract no. 122522g, I. S. SHUL'GA ET AL.: "Synthesis of 6-Nitrodiphenylamine-2-carboxylic acid Derivatives, their Physiochemical and Antimicrobial Properties" page 65; column 1; XP002081074 see abstract & FARM. ZH., vol. 27, no. 3, 1972, pages 84-85, kiev ---	1
X	CHEMICAL ABSTRACTS, vol. 114, no. 19, 13 May 1991 Columbus, Ohio, US; abstract no. 184706m, A. N. GAIDUKEVICH ET AL.: "Reactivity of Derivatives of Phenylanthranilic Acid. VII. Acid-base Properties of Derivatives of Phenylanthranilic Acid in Binary Solvent Dioxane-Water" page 714; column 1; XP002081075 see abstract -& CHEMICAL ABSTRACTS 12TH COLLECTIVE INDEX., vol. 106-115, 1987 - 1991, page 14641cs XP002081069 COLUMBUS US see column 2, line 44 - line 47 & ORG. REACT. TARTU), vol. 27, no. 1-2, 1990, pages 87-96, ---	1
X	CHEMICAL ABSTRACTS, vol. 109, no. 17, 24 October 1988 Columbus, Ohio, US; abstract no. 149000b, I. S. SHUL'GA ET AL.: "Synthesie and Phisiochemical and Biological Properties on Diphenylamine-2-carboxylic Acid Derivatives" page 682; column 1; XP002081076 see abstract -& CHEMICAL ABSTRACTS 12TH COLLECTIVE INDEX., vol. 106-115, 1987 - 1991, page 15109cs XP002081070 COLUMBUS US see column 2, line 38 - line 41 & FARM. ZH. (KIEV), no. 1, 1988, pages 42-45, ---	1
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/13105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 101, no. 3, 16 July 1984 Columbus, Ohio, US; abstract no. 22893z, V. I. MAKURINA ET AL.: "A Study of Acid-base Equilibria in Aqueous Dioxane Solutions of Phenanthranyl Acid Derivatives" page 549; column 2; XP002081077 see abstract -& CHEMICAL ABSTRACTS 11TH COLLECTIVE INDEX., vol. 96-105, 1982 - 1986, page 10688cs XP002081071 COLUMBUS US see column 2, line 12-14 see column 2, line 23 - line 25 see column 2, line 34 - line 39 & ORG. REACT (TARTU), vol. 20, no. 3, 1983, pages 311-315, ---	1
X	CHEMICAL ABSTRACTS, vol. 83, no. 3, 21 July 1975 Columbus, Ohio, US; abstract no. 27831x, JACEK ROMANOWSKI ET AL.: "Use of 2,6-Dichlorobenzonitrile (Dichlobenil) as a Starting Substance for Synthesizing Herbicides Derived from Benzoic Acid" page 473; column 1; XP002081078 see abstract -& CHEMICAL ABSTRACTS 9TH COLLECTIVE INDEX., vol. 76-85, 1972 - 1976, page 6385cs XP002081072 COLUMBUS US see column 3, line 28 - line 29 & PRZEM. CHEM., vol. 54, no. 1, 1975, pages 26-31, warsaw, poland ---	1
A	US 5 525 625 A (ALEXANDER J. BRIDGES ET AL.) 11 June 1996 see the whole document -----	1-34

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23-34
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 23-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte onal Application No
PCT/US 98/13105

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9837881 A	03-09-1998	NONE	
US 2077249 A	13-04-1937	NONE	
US 5525625 A	11-06-1996	AU 690400 B	23-04-1998
		AU 4245696 A	14-08-1996
		CA 2208075 A	01-08-1996
		EP 0805807 A	12-11-1997
		WO 9622985 A	01-08-1996